

Appl. No. 09/975,317  
Amendment dated: August 27, 2003  
Reply to OA of: May 1, 2003

### **REMARKS**

The title of the invention has been amended and it is believed that this amendment obviates the objection to the specification.

This application contains drawings and it is most respectfully requested that the Examiner confirm in the next Official Action that the drawings are acceptable.

All of the claims in the application have been canceled and replaced with a new set of claims basically paralleling the canceled claims but containing additional information for purposes of clarification and to further distinguish over the prior art. The new claims are claims 51-74. These claims are fully supported by Applicants' specification. Applicants most respectfully submit that all the claims now present in the application are in full compliance with 35 U.S.C. §112 and are clearly patentable over the references of record.

The rejection of claims 47-50 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been carefully considered but is most respectfully traversed.

The Examiner objects to the use in claims 47 to 50 of the wording "subjecting said body to a magnetic resonance imaging procedure as defined in claim 31" because the method of MRI in claim 31 already requires the administration of a contrast agent, subjecting a body to MRI, and providing a series of images. It appears that the Examiner is of the opinion that this reference to claim 31 is intended to bring in all the limitations of the claim referred to. This is not what was intended when drafting these claims and as a matter of language this interpretation is not consistent with the wording of the claims. Consequently, Applicants do not agree with this objection. However, in order to save the expense of arguing against the objection, claims 47 to 50 have been amended. In each claim, the wording referred to above has been replaced with "subjecting said body to a magnetic resonance imaging procedure capable of generating images with time intervals of less than 0.5 seconds" (as found in claim 31). Applicants trust this is acceptable under US practice. Accordingly, it is most respectfully

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requested that this rejection be withdrawn in view of the cancellation of claims 47-50 and the above comments.

The rejection of claims 31-33, 35-40 and 46-50 under 35 U.S.C. 102(b) as being anticipated by Ericcson (WO 95/02831, US 5,869,023 used as an equivalent). The rejection based on Ericcson '023 has been carefully considered but is most respectfully traversed in view of the amendments to the claims.

The methods disclosed in Ericcson and the present application are in essence quite different as would be appreciated by one of ordinary skill in the art to which the invention pertains. Ericcson discloses the use of both a first and a second paramagnetic contrast agent, whereas the present invention relates to the use of a single manganese contrast agent. It is believed that the Examiner has appreciated this difference but it is a matter of claim interpretation that this difference is reflected in the claims. The Examiner maintains that the wording of present claim 31 does not appear to exclude the use of additional contrast agents as in Ericcson and the Examiner's interpretation of claim 31 appears reasonable. Consequently, in order to more clearly distinguish the present invention from the method disclosed in Ericcson, claim 31 has been canceled and rewritten as claim 51 which has been limited to "A method of detecting myocardial ischemia in a human or non-human body, said method comprising administering to said body a contrast medium consisting essentially of a manganese complex or salt thereof...". Applicants most respectfully submit that this amendment is implicitly supported by the present specification as would be appreciated by one of ordinary skill in the art and further distinguishes the claimed invention over the prior art.

Ericcson teaches the use of a first and a second paramagnetic contrast agent where one contrast agent is a positive contrast agent and the other is a negative contrast agent. It is therefore essential in the method taught in Ericcson to use a negative contrast agent, i.e. a complex of Tb, Sm or Dy (see col. 6, lines 64-65). The present application is now limited to a method using a contrast medium consisting essentially of a manganese complex or salt thereof and therefore excludes methods using additional contrast agents. The present invention is therefore novel over Ericcson. Accordingly, it is most respectfully requested that this rejection be withdrawn.

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The rejection of claims 31-33 and 35-46 under 35 U.S.C. 103(a) as being unpatentable over Edelman '123 in view of Rocklage '931 and the rejection of claims 31-33, 35-40 and 46-50 as being unpatentable over Edelman '123 in view of Ericsson '023 has been carefully considered. Each rejection is most respectfully traversed.

The Examiner raises an obviousness rejection over Edelman in light of Rocklage. Applicants most respectfully submit that the Examiner has failed to take into account the respective teachings of the two documents and is wrong to conclude that the skilled person would have been led to the present invention in light of the teaching of these two documents. This rejection appears to be based on hindsight and does not interpret the prior art as it would be interpreted by one of ordinary skill in the art to which the invention pertains.

The presently claimed invention relates to a combination of a contrast medium consisting essentially of a manganese complex or salt thereof at specified, low doses with a specific imaging technique capable of generating images with short time intervals. One of ordinary skill in the art would have had no motivation to perform this combination of features with a reasonable expectation of success in light of Edelman and Rocklage. Edelman discloses fast-imaging techniques as defined in the present application. However, the MRI-contrast agents disclosed in Edelman are Gd-DTPA and iron oxides. There is no reference or suggestion to use manganese chelates as contrast agents or to the doses of the contrast agents suitable for use in such a technique. Furthermore, there is no hint in Edelman to use any contrast agent other than Gd or iron complexes. Therefore, the skilled person would have considered using only Gd and iron complexes when carrying out the methods disclosed in Edelman. The Examiner comments that Edelman fails to disclose the use of the same contrast agents as claimed in the present application. However, in light of Rocklage, the Examiner is of the opinion that the present application is obvious. Applicants do not consider this mosaic proper. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps."). Accordingly, it is most respectfully requested that this rejection be withdrawn.

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The rejection of claim 34 under 35 U.S.C. 103(a) as being unpatentable over Edelman in view of Rocklage, as applied to claims 31-33 and 35-46 above, in further view of Goldenberg '968 and claim 34 over Edelman in view of Goldenberg has been carefully considered but is most respectfully traversed.

For imaging methods as disclosed in Edelman and claimed in the present application, there is a relationship between signal interval and T1, in that the signal intensity from a particular tissue region is controlled by both T1 for that region and the interval time used in the technique. The addition of contrast agent to a particular tissue region shortens the T1 of this region and consequently the interval time employed can be made shorter without loss of signal intensity. Conversely, shortening the interval time without a reduction in T1, for instance where a contrast agent has not been taken up, suppresses signal intensity. This principle forms the basis of how these fast-imaging techniques are useful. Consequently, when the interval time is reduced, regions with contrast agent will have a reduced T1 and are able to produce a signal. Regions with no contrast agent will have a longer T1 and conversely when the interval time is reduced will produce little or no signal.

Fast imaging techniques are useful to identify regions that take up specifically designed contrast agent and those that do not. T1 is directly affected by the concentration of paramagnetic centres in the tissue which is to be imaged. Consequently, it would not have been prima facie obvious that lowering the dose of a manganese complex, i.e. reducing a source of paramagnetic centres that shortens T1, would result in significant contrast enhancement using fast-imaging techniques involving short interval times. The present invention is based on the finding that one can decrease the risks involved when using manganese complexes by administering a lower dose of complex and still obtain effective myocardial imaging with fast or ultra-fast MRI techniques.

There is no reference in the Rocklage patent to the fast-imaging techniques claimed in the present application. Furthermore, there is no suggestion in Rocklage that the manganese complexes disclosed therein are of use in the imaging of the myocardium. On the other hand, the use of manganese in the present invention distinguishes it from that of Edelman. The use of manganese in detecting myocardium

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ischemia has advantages which are nowhere taught or suggested in the prior art. Manganese enters into intercellular space since it has access to the cardiomyocytes via slow  $\text{Ca}^{2+}$  channels whereas Gd-DTPA distributes into the extracellular fluid space. The advantages of manganese for this reason in methods for detecting myocardial ischemia are discussed in the description (see the passage bridging pages 2 and 3).

There is no suggestion in either Edelman or Rocklage that, firstly, manganese complexes would be of use in fast-imaging techniques and, secondly, that the manganese complexes claimed in the invention would work as well as they do at low doses in detecting myocardial ischemia. Furthermore, the skilled man would believe that such doses would not produce clinically relevant or useful images. Applicants most respectfully submit that this combination of the fast-imaging techniques of the present invention and the use of manganese complexes at low doses for detecting myocardial ischemia was not obvious to the person skilled in the art.

The Examiner relies on Goldenberg for a disclosure of an inversion recovery echo planar imaging procedure. This is a conventional procedure. Applicants most respectfully submit that in light of the above comments, the subject-matter of claim 51 is novel and inventive over the prior art and that Goldenberg adds nothing in this respect.


The Examiner also alleges that claim 31, now new claim 51, is obvious over Edelman in light of Ericcson. It is submitted that the combination of any document and Ericcson would have led the skilled person to a method which contains both a positive contrast agent and a negative contrast agent since the presence of the two contrast agents is essential in Ericcson. Following the amendment to claim 31 described above, any such method would not fall within the scope of new claim 51. Claim 51 is therefore inventive over any combination of documents including Ericcson and the rejection should be withdrawn.

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In view of the above comments and further amendments to the specification and claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,

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